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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/003,462 | 12/06/2001 | Aillette Mulet Sierra | 30797-717.201 | 4354 |

21971 7590 04/01/2008
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| EXAMINER | |
|---|---|
| HOLLERAN, ANNE L | |
| ART UNIT | PAPER NUMBER |
| 1643 | |
| MAIL DATE | DELIVERY MODE |
| 04/01/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/003,462 | SIERRA ET AL. | |
| | Examiner | Art Unit | |
| | ANNE L. HOLLERAN | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,4-7 and 12-18* is/are pending in the application.

4a) Of the above claim(s) *14-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/08/2008 has been entered.

Clams 1, 2, 4-7, 12-18 are pending. Claims 14-18, drawn to non-elected inventions, are withdrawn from consideration. Claims 1, 2, 4-7, 12 and 13 are examined on the merits.

The second declaration of Belinda Sanchez Ramirez, filed under 37 C.F.R. 1.131, is acknowledged and has been considered.

***Claim Rejections Withdrawn:***

The rejection of claims 1, 2, 7, and 12 under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Gonzalez (Gonzalez, S. et al, Scandinavian J. Immunol., 52: 113, 2000, August) for the reasons of record is withdrawn in view of the second declaration of Belinda Sanchez Ramirez filed 2/8/2008.

The declaration filed on 2/8/2008 under 37 CFR 1.131 is sufficient to overcome the Gonzalez-2000 reference.

The rejection of claims 1, 4-6, 12 and 13 under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Gonzalez (Gonzalez, S. et al, Scandinavian J. Immunol., 52: 113, 2000, August) and further in view of Gonzalez-1997 (of record) for the reasons of record.

The declaration filed on 2/8/2008 under 37 CFR 1.131 is sufficient to overcome the Gonzalez-2000 reference.

***New Grounds of Rejection:***

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Davila (US 5,894,018; issued Apr. 13, 1999) and further in view of Rodriquez (US 5,286,484; issued Feb. 15, 1994).

Hoeprich teaches a conjugate of human TGFα and keyhole limpet hemocyanine, coupled using gluteraldehyde (see page 19087, 1st column). The TGFα was either chemically synthesized or recombinantly synthesized (see Figure 2 on page 19088 and page 19087, 1st column). The resulting conjugate was immunogenic (see Figure 2, and page 19088, 1st column). The adjuvant used was Freund's complete adjuvant (see page 19087, 2nd column), and also Freund's incomplete adjuvant (see 19087, 1st column). Hoeprich fails to teach a conjugate of human TGFα and P64k. However, Davila teaches a vaccine composition comprising EGF conjugated to P64k. Further, Rodriquez teaches that P64k may be used in vaccine prepaations with a broad immunoprotection spectrum. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have altered the conjugate taught by Hoeprich in view of the teachings of Davila and Rodriquez to make the claimed inventions. One would have been motivated to make a conjugate with hTGFα with P64k because of the teachings of Davila showing its successful use in a conjugate with EGF (see column 10, line 55 – column 11, line 20), and because of the teachings of Rodriquez that the P64K antigen is useful in vaccine preparations (see column 8, lines 20-25).

Claims 1, 2, 4, 5, 7, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Davila (US 5,894,018; issued Apr. 13, 1999), in view of Rodriquez (US 5,286,484; issued Feb. 15, 1994), and further in view of Gonzalez-1997 (of record).

Within the scope of the claims are vaccine compositions comprising fusion proteins between hTGFα and P64k. Although claim 7 recites conjugation by a chemical method, this is broadly interpreted to encompass recombinant fusion proteins. The combination of Hoeprich, Davila and Rodriquez suggests a P64k carrier protein linked to hTGFα by gluteraldehyde linkage, but fails to suggest a recombinant fusion protein combining hTGFα and P64k. However, the use of recombinant fusion proteins comprising tumor associated antigens such as EGF, a ligand that binds EGFR, and P64k is known in the art as evidenced by Gonzalez-1997, wher the fusion protein is cloned in an expression vector of bacteria and expressed in E. coli (see page 92). Further, the use of adjuvants such as $Al(OH)_3$ is known in the art as evidenced by Gonzalez-1997 (page 94). Gonzalez-1997 teaches that a fusion protein has similar results to a chemically conjugated immunogen in the treatment of tumor bearing mice, but that a fusion protein has advantages in that production of the fusion protein may be scaled up reproducibly (see pages 97 and also 99). Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the combined teachings of Hoeprich, Davila, Rodriquez and Gonzalez-1997 to make the claimed fusion proteins. One would have been motivated to make a fusion protein comprising hTGFα of Hoeprich linked to P64k as taught by Davila, Rodriquez and Gonzalez-1997 because Gonzalez-1997 teaches that a fusion protein has advantages over a chemical conjugate.

Claims 1, 2, 4-7, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeprich (of record) in view of Davila (US 5,894,018; issued Apr. 13, 1999), in view of Rodriquez (US 5,286,484; issued Feb. 15, 1994), in view of Gonzalez-1997 (of record), and further in view of Ritzenthaler (Ritzenthaler, C. et al., J. General Virology, 76: 907-915, 1995).

Within the scope of the claims are vaccine compositions comprising fusion proteins between hTGFα and P64k, where the expression vector of bacteria presents a genetic sequence coding for six histidines. Although claim 7 recites conjugation by a chemical method, this is broadly interpreted to encompass recombinant fusion proteins. The teachings of Heoprich, Davila, Rodriquez and Gonzalez-1997 are set forth above. The combination of Hoeprich, Davila, Rodriquez and Gonzalez-1997 is silent with respect to a bacterial expression vector that allows for making a six histidine fusion protein. However, the use histidine tags for purification of recombinantly produced proteins is known in the art as evidenced by the teachings of Ritzenthaler. Ritzenthaler teaches that to achieve large scale production and easy purification the P38 protein was expressed in E. coli as a fusion protein fused to six histidines (see page 909, first column). Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have altered the expression vector of Gonzalez-1997 to include a six histidine tag to achieve large scale production and easy purification as suggested by Ritzenthaler.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The

examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
March 29, 2008

/Alana M. Harris, Ph.D./
Primary Examiner, Art Unit 1643